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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/855,587	05/16/2001	Yoshiki Sasai	00766.000044	1416

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EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/855,587	SASAI ET AL.	
	Examiner	Art Unit	
	MAGDALENE K. SGAGIAS	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,15,18-21,23,24,72,74,75 and 80-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,15,18-21,23,24,72,74,75 and 80-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 11/16/07 have been fully considered but they are not persuasive. The amendment has been entered. Claims 1, 15, 18-21, 23-24, 72, 74-75, 80-87 are pending and under consideration. Claims 2-14, 16-15, 22, 25-71, 73, 76-79 are canceled.

The declaration under 37 C.F.R. & 1.132 has been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 15, 18-21, 23-24, 72, 74-75, 80-87 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record in the office action mailed on 10/4/07. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants argue claims 82-87 are amended more specifically to recite the subject matter of the present invention.

These arguments are not persuasive because the amendment of claims 82-87 from the "cell is" to "method produces" while it makes the claims to refer to the preamble of the independent claim 1 rather than to a method step of claim 1, however, this amendment has no impact on claims interpretation and thus does not obviate the rejection under 35 USC 112 first

paragraph written description requirement, because said amendment has not changed any structural or functional characteristics or enablement rejections as cited in the non-final office action mailed on 10/4/07.

Applicants argue and have submitted a Declaration under Rule 132 of Dr. Hiromasa Miyaji addressing the Examiner's prior concerns in the December 28, 2006 Advisory Action. Applicants argue to overcome the claim 81 rejection under 35 USC 102(b) as being anticipated by Thompson, because even though Thompson uses mouse embryonic fibroblasts as feeder cells the claimed invention does not preclude the use of any stroma cell which is recognized by a monoclonal antibody produced by hybridoma FERM BP-7573". Applicants argue in Dr. Miyaji's Declaration, Applicants' experiments provide conclusive evidence that Thompson's mouse embryonic fibroblast cells do not express KM 1310 antigen and are not recognized by a monoclonal antibody produced by FERM BP-7573.

A. Regarding Applicant's response to the advisory action Applicants provided evidence that Thomson's feeder cell fibroblasts are not recognized by the Applicant's hybridoma produced by FERM BP-7573 are convincing and the Examiner agrees that Applicant's feeder cells are distinct from the feeder cells used by Thomson in the art rejection under 35 USC 102(b) for claim 81 in the final office action mailed on 7/19/06. As such the currently presented Dr. Miyaji's Declaration, indeed provide conclusive evidence that Thompson's mouse embryonic fibroblast cells do not express KM 1310 antigen and are not recognized by a monoclonal antibody produced by FERM BP-7573 and overcome the rejection under 35 USC 102(b) of the final office action mailed on 7/19/06. However, after the mailing of the Advisory Office Action, Applicants have amended independent claims 1, 80 and 81, which raised new issues under 35

USC 112, 1st paragraph, written description and enablement rejections as discussed in the currently pending non-final office action mailed on 10/4/07.

B. To the extent that the claimed methods are not described in the instant disclosure, claims 1, 15, 18-21, 23-24, 72, 74-75, 80-87 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention since a disclosure cannot teach one to make or use something that has not been described is maintained for the reasons of record in the office action mailed on 10/4/07.

Applicants argue that page 30, lines 27-30 explicitly teaches that “Examples of the nervous system cell include a neural cell, a nerve cell, a cell of neural tube, a cell of neural crest and the like" and these cells are explained in with greater particularity from page 33, line 33 to page 34, line 27.

These arguments are not persuasive because, the specification in the above pages explains that neural induction commences from a primitive streak in the primitive ectoderm layer; neuroectoderms become a neural plate independent from an epidermal ectoderm and then form a neural tube by invagination into the ventral side; and during invagination the ectoderm portion between the neural plate and the epidermal ectoderm forms a neural crest, in vivo. However, this induction of neural tube and neural crest from the primitive streak in the development of chordates in vivo, does not provide sufficient guidance for culturing an embryonic stem cell in vitro under the culture conditions as required in the independent claim 1, 80 or 81 resulting in the production of a neural crest cell or a neural tube cell of claim 1 or a dopaminergic neuron, an acetylcholinergic neuron, a gamma-aminobutyratergic neuron or a serotonergic neuron of claim 80; or a neural stem cell which is stained by an anti-nestin

antibody of claim 81. The primitive streak in the development of chondrates and its evolution into a neural tube and neural crest in vivo upon various factors including factor Shh and BMP4 resulting in the formation of neural tube and neural crest respectively in vivo cannot be correlated to the in vitro culture of the claimed cells as climed in the instant case. For example, the effect of the Shh or BMP4 factors in vivo cannot be correlated to the in vitro culture condition because in vivo these factors are influenced by the structure of the neural tube and the neural crest as neural induction commences from the primitive streak and gradually evolves into neural tube and neural crest unlike the in vitro culture lacking such primitive structure to result in the evolution of the claimed specific neural cells during the evolution of the primitive streak into the neural tube and neural crest.

C. Applicants argue in examples 1 and 14 that nervous system cells expressing not only the NCAM as a neuron marker but also various types of neuron-specific markers are formed by the nerve cell induction of the ES cell by its coculturing with the PA6 cell. That is, when the ES cell was differentiation-induced by coculturing with the PA6 cell, it is differentiation-induced into a nervous system cell which is positioned on the basal plate of the most ventral side of the central nervous system primordium (neural tube) and expresses HNF-3beta, a nervous system cell which is positioned secondary to the HNF-3beta from the ventral side of the central nervous system primordium (neural tube) and expresses Nkx2.2, a nerve cell of the neural tube dorsal side expressing Pax-7, a neural crest cell expressing AP-2 and a motor neuron expressing islet 1. Applicants argue since shh and BMP4, whose relation to the determination of dorso-ventral axis during the embryo neurogenesis has been revealed, showed a differentiation potency similar to the in vivo differentiation potency of embryonic neural precursor cell, a cell of neural tube before the step of determining dorso-ventral axis is induced by coculturing ES cell with the PA6 cell. That is, in this neural tube cell, expression induction of

the ventral side markers HNF-3.beta and Nkx2.2 and expression inhibition of the dorsal side markers Pax-7 and AP-2 are observed by the action of shh as a neural tube dorso- ventral factor. On the other hand, when the BMP4 as a neural tube dorsal side factor is allowed to act, expression inhibition of the ventral side markers HNF-3.beta and Nkx2.2 and expression induction of the dorsal side markers Pax-7 and AP-2 are observed. Applicants argue example 14 explicitly shows producing neural tube and neural crest cells upon coculturing embryonic stem cells with stroma cells in the manner recited in the pending claims. By the foregoing, it is apparent all the steps recited in claim 1 are all well-taught in the specification as filed.

These arguments are not persuasive because in examples 1 and 14, the co-culture of the EB5 ES cell line with the PA6 stroma cells resulting in the production of cells with the above neural markers cannot be correlated to the in vivo differentiation-induction into a nervous system cell which is positioned on the basal palate of the most ventral side of the nervous system primordium (neural tube) and expresses HNF-3beta, a nervous system cell which is positioned secondary to the HNF-3beta from the ventral side of the central nervous system primordium (neural tube) and expresses Nkx.2, a nerve cell of the neural tube dorsal side expressing Pax-7, a neural crest cell expressing AP-2 and a motor neuron expressing islet 1. The specification teaches the term "cell of neural tube" means a cell which constitutes a neural tube in the generation process of neural tube in the initial stage of development in chodrates [0192] and the term "cell of neural crest:" means a cell which constitutes a neural crest in the above generation process [0193]. However, applicants failed to provide guidance to correlate the induction of differentiation of embryonic stem cells into neural cell expressing neural surface markers into a neural crest cell or a neural tube cell that morphologically, physiologically or structurally meets the limitations of a neural tube or a neural crest cell. The mere expression of neural surface markers on the differentiated embryonic stem cells of the disclosed invention

cannot support the morphological, structural and physiological limitations of these cells in the generation process of a neural crest or neural tube. **Mizuseki et al,** (PNAS, 100(10): 5828-5833, 2003) notes it remains to be known whether ES cell-derived neural precursors generated in vitro can produce the full dorsal-ventral range of neuroectodermal derivatives in response to embryonic positional information (p 5828, 1st column, 3rd paragraph). Further, the instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of producing the full dorsal-ventral range of neuroectodermal derivatives in response embryonic positional information raised by the state of the art. Therefore, the skilled artisan would conclude that the state of art of producing neural crest cell or neural tube cell is undeveloped and unpredictable at best. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for producing these cells without a reasonable expectation of success.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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/Anne-Marie Falk/
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